REMARKS

Status of the claims:

With the above amendments, claim 13 has been canceled and claims 7, 10, and 11 have been amended. Thus, claims 7-12 are pending and ready for further action on the merits. No new matter has been added by way of the above amendments. The claims have been amended to correct spelling mistakes or to comply with the Examiner's suggestions. Reconsideration is respectfully requested in light of the following remarks.

Claim Objections

Claims 7 and 13 are objected to for informalities. The Examiner asserts that "chloricromene" is misspelled. Applicants submit that the correct spelling is "cloricromene" and thus, claim 7 has been amended accordingly. In claim 13, Applicants believe that this term is spelled correctly. Withdrawal of the objection is warranted and respectfully requested.

Rejections under 35 USC §112, second paragraph

Claims 7-12 have been rejected under 35 USC §112, second paragraph as being indefinite. The Examiner asserts that the claims as they currently stand are indefinite. Applicants have amended claim 7 to recite "A method of treating hypercholesterolaemia in a patient in need thereof comprising

administering to said patient a pharmaceutically acceptable amount of a composition comprising cloricromene or a cloricromene salt thereof" in accordance with the Examiner's suggestion. Applicants believe that with this amendment that the rejection has been obviated. Withdrawal of the rejection is warranted and respectfully requested.

Regarding claim 10, the Examiner has suggested amending the claim to recite "a patient" instead of "patients". Applicants have amended the claim accordingly. Withdrawal of the rejection is warranted and respectfully requested.

Regarding claim 11, the Examiner has suggested omitting "controlled release systems" and amending capsules, tablets, injectable solutions, and transdermal systems to recite the singular of each of these. Applicants have amended the claim accordingly. Withdrawal of the rejection is warranted and respectfully requested.

Rejections under 35 USC §103

Claims 7-11 are rejected under 35 USC §103(a) as being unpatentable over Hoult et al. (Hoult et al., Pharmacological and Biochemical Actions of Simple Coumarins: Natural Products with Therapeutic Potential, Gen. Pharmac. Vol. 27, No. 4, pp. 713-722 (1996)).

This rejection is traversed for the following reasons.

Present Invention

The present invention, as recited in independent claim 7, relates to a method of treating hypercholesterolaemia in a patient in need thereof comprising administering to said patient a pharmaceutically acceptable amount of a composition comprising cloricromene or a cloricromene salt thereof.

Disclosure of Hoult et al.

Hoult et al. disclose hypocholesterolemizing for only one compound, scoparone.

Removal of the Rejection over Hoult et al.

As mentioned above, Hoult et al. disclose hypocholesterolemizing for only one compound, scoparone. Scoparone has a very different chemical structure than cloricromene. Moreover, the mechanism of action of scoparone is vastly different in its physiological and clinical characteristics.

Hoult et al. show that coumarins and derivatives thereof can have very different pharmacological properties and characteristics (please see Table 1 in Hoult et al.) so that not even those that are skilled in the art would or could predict that two different coumarins could have the same biochemical and pharmacological characteristics.

As to the differences between antithrombotic and anti-hypercholesterolaemic drugs, the two activities are actually unrelated so that, for example, well-known anti-cholesterol drugs such as statins lack any antithrombotic activity and antithrombotic drugs such as acetylsalicylic acid or clopidogrel do not even minimally affect cholesterol levels. This is well known by those of ordinary skill in the art.

Applicants after an investigative and intensive search of drugs, discovered only one anti-cholesterol compound, "clofibrate" that is also known to have some activity on platelet function. However, Applicants attach a reference from Goodman and Gilman's "The Pharmacological Basis of Therapeutics", VII Edition, wherein it is reported that "its (i.e., clofibrate) use as an antithrombotic agent" cannot be recommended.

Thus, as explained above, one of skill in the art would never assume that an antithrombotic compound could be used for anti-hypercholesterolaemic (or vice versa). For the above reasons, the rejection is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Regarding the Examiner's assertion that Hoult et al. disclose that coumarins are known to reduce cholesterol, Applicants were unable to find this general teaching in Hoult et al. Applicants

note that at page 715, left hand column, fourth full paragraph, Hoult et al. conclude the paragraph by saying

> *We will attempt to illustrate the wide range of pharmacological and biochemical properties now attributable to coumarins, but will emphasise how these exhibit structure dependency.*

Thus, Applicants are of the opinion that there is no general teaching in Hoult et al. that coumarins are known to reduce cholesterol. It also appears that Hoult et al. recognized that a compound's activity is very much dependent on its structure. Thus, for the above reasons, Applicants submit the rejection is inopposite. Withdrawal of the rejection is warranted and respectfully requested.

Allowable Subject Matter

Applicants would like to thank the Examiner for acknowledging that claim 12 is allowable.

Conclusion

With the above remarks and amendments, it is believed that the claims, as they now stand, define patentable subject matter such that passage of the instant invention to allowance is warranted. A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, T. Benjamin Schroeder (Reg. No.

50,990), in the Washington metropolitan area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
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Attachment(s): Selection from Goodman and Gilman's "The Pharmacological Basis of Therapeutics", VII Edition.

GOODMAN and GILMAN's The Pharmacological Basis of Therapeutics

SEVENTH EDITION

MACMILLAN PUBLISHING COMPANY
New York
COLLIER MACMILLAN CANADA, INC.
Toronto
COLLIER MACMILLAN PUBLISHERS
London

Dextran 70 and Dextran 75. These substances, which are used as plasma expanders, are partially hydrolyzed polymers of glucose that are obtained from the bacterium *Leuconostoc mesenteroides* (*see* Chapter 35). Dextran added to blood *in vitro* has no effect on platelet function; however, the bleeding time, polymerization of fibrin, and platelet function may be impaired *in vivo*. Infusions of dextran increase the colloidal osmotic pressure, which necessitates care in their use in patients with pulmonary edema, congestive heart failure, and decreased renal function. Dextran-induced formation of rouleaux interferes with blood typing, cross matching, and Rh testing, which requires the performance of those tests on blood obtained before dextran infusion. Dextran is contraindicated in patients with significant anemia, severe thrombocytopenia, and reduced concentrations of fibrinogen in plasma. Side effects include occasional urticaria, wheezing, a feeling of tightness in the chest, mild hypotension, and, rarely, severe anaphylaxis. Dextran continues to be studied in randomized double-blind trials for efficacy in the prevention of postoperative thromboembolic disease in surgical patients (*see* Ljungström, 1983). *Dextran 70* (MACRODEX) and *dextran 75* (DEXTRAN 75, GENTRAN 75) are available as a 6% injection with 5% dextrose solution or as a 6% injection with 0.9% sodium chloride solution.

Dazoxiben. This drug, which is an analog of imidazole, selectively inhibits thromboxane synthetase and thereby prevents the formation of TXA_2, a powerful stimulator of platelet aggregation. Dazoxiben markedly inhibits the synthesis of TXA_2 *in vitro*, but does not prevent platelet aggregation unless low doses of aspirin are added to the regimen. The concomitant administration of aspirin appears to inhibit the accumulation of products of the fatty acid cyclooxygenase reaction that occurs during blockade of TXA_2 synthesis; these products can stimulate platelet aggregation (Bertelé *et al.*, 1983). Dazoxiben and other inhibitors of thromboxane synthetase are currently being studied in clinical trials.

Ticlopidine. This drug is a thienopyridine that alters platelet membranes directly, independent of any effect on prostaglandins. It inhibits platelet aggregation and secretion, reduces deposition of platelets and fibrin on artificial surfaces, and prolongs the bleeding time. Ticlopidine has been introduced in Europe, and it is now undergoing clinical trials in the United States. It may be useful in extracorporeal circulation (*see* Symposium, 1983).

Clofibrate. Clofibrate is a hypolipidemic drug that may reduce platelet adhesiveness *in vitro* and increase abnormally short survival of platelets in some patients with coronary artery disease. Previous favorable results with clofibrate in patients with angina pectoris have not been confirmed in a large, randomized clinical trial in patients who had suffered a myocardial infarction (Coronary Drug Project Research Group, 1975). Its use as an antithrombotic agent cannot be recommended. The use of clofibrate in the treatment of hyperlipoproteinemias is discussed in Chapter 34.

THROMBOLYTIC DRUGS

Streptokinase and urokinase are proteins that have demonstrated efficacy for the treatment of acute thromboembolic disease. They promote the dissolution of thrombi by stimulating the activation of endogenous plasminogen to *plasmin* (fibrinolysin), a proteolytic enzyme that hydrolyzes fibrin (*see* Figure 58–3). Because these drugs can profoundly alter hemostasis, they should be used only by physicians who have had extensive experience in the management of thromboembolic disease. Two new approaches may reduce the adverse systemic effects of such therapy. Intra-arterial use of a fibrinolytic drug (*e.g.*,

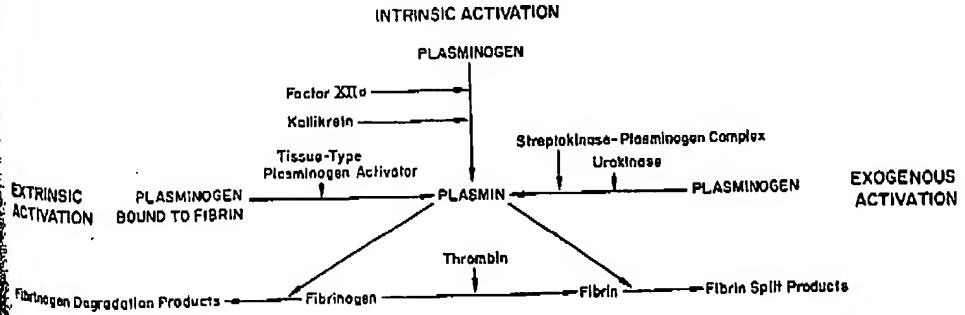

Figure 58–3. *Schematic representation of the pathways for activation of plasminogen and for the lysis of fibrinogen and fibrin.*